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Prospects for Management of Gastrointestinal Injury Associated With the Acute Radiation Syndrome

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The effect of total-body ionizing radiation on the digestive tract is dose-dependent and time-dependent. At low doses (1.5 Gy), one observes only a short prodromal syndrome consisting of nausea, vomiting, and gastric suppression. At doses >6 Gy, the prodromal syndrome is more marked, and it is followed after a 2–5-day remission period by a subacute syndrome, characterized by diarrhea and hematochezia. This gastrointestinal syndrome is superimposed onto a radiation-induced bone marrow suppression. The combination of intestinal and hemopoietic syndromes results in dehydration, anemia, and infection, leading eventually to irreversible shock and death. The treatment of prodromal symptoms is based on the administration of antiemetics and gastrokinetics, although an effective treatment devoid of side effects is not yet available for human therapy. The treatment of the gastrointestinal subacute syndrome remains difficult and unsuccessful after exposure to total body doses >8–10 Gy. Supportive therapy to prevent infection and dehydration may be effective if restoration or repopulation of the intestinal and bone marrow stem cells does occur. In addition, bone marrow transplantation may improve the prospect of treating the hemopoietic syndrome, although the experience gained in Chernobyl suggests that this treatment is difficult to apply in the case of nuclear accidents. Administration of radioprotectants before irradiation decreases damage to healthy cells, while not protecting cancerous tissues. In the future, stimulation of gastrointestinal and hemopoietic progenitor cells may be possible using cell growth regulators, but much remains to be done to improve the treatment of radiation damage to the gastrointestinal tract.

During the past 30 yr, much has been learned about the physiologic mechanisms causing radiation injury, and the recent events in Chernobyl have heightened the general awareness to nuclear hazards. The medical experience in Russia should alert physicians that high-dose total-body radiation injury can occur and we must be prepared to treat such injuries.

The first comprehensive description of the acute radiation syndrome in humans was provided by Hempelmann and colleagues (1) based on the experience they acquired while treating 10 patients involved in two radiation accidents at Los Alamos National Laboratory on August 21, 1945, and on May 21, 1946. These cases pointed out the complexity of the pathophysiology of radiation injury.

In his classic 1956 paper, Quastler (2) hypothesized that total-body irradiation arrests the production of new epithelial cells from the crypts of Lieberkuhn. The diminished replacement of epithelial cells combined with normal sloughing of differentiated cells leads to the depletion of mature intestinal surface epithelial cells. This loss of epithelial cells causes a breakdown of the barrier between the intestinal luminal contents and permits entry of toxic substances into the systemic circulation, which can be lethal. In addition, as discussed by Moore (3), changes of the metabolic balance observed after total-body irradiation may bear similarities with those seen after surgical injury. In both situations, there is an increase in the extracellular component at the expense of intracellular metabolism, increased urinary nitrogen excretion, loss of nitrogen and potassium, and a tendency to retain sodium.

In 1965, Bond and his colleagues (4) reviewed the accumulated human and animal experience; they postulated a disturbance of cellular kinetics in multiple-organ systems that manifested itself in distinct components: the hemopoietic syndrome, the gastro-

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intestinal syndrome, and the cardiovascular or central nervous system syndrome. They also recognized that the acute radiation syndrome is characterized by an acute phase, also called prodromal syndrome, and a subacute phase, also called bone marrow and gastrointestinal syndromes. These two phases of radiation sickness are separated by an apparent remission during which the patient may be completely symptom-free.

Although we recognize that bone marrow depression with its hematologic and immunologic sequelae is of extreme importance and represents a medical problem frequently encountered in irradiated persons, we have elected to review specifically the less commonly considered gastrointestinal component of the acute radiation syndrome. The large amount of information on the pathophysiology of radiation-induced gut dysfunction is summarized along with its implications for current and future therapeutic intervention. The long-term effects of radiation (such as enteropathy, fibrosis, and carcinogenesis) will not be considered here, and the reader is referred to the reviews by Morgenstern et al. (5) and Fry (6).

It must be remembered that the degree of gastrointestinal injury following irradiation will depend upon a variety of conditions. For example, many of the side effects described in this review are not observed after exposure to similar doses during local irradiation or in preparation for bone marrow transplantation. It is not known whether this is entirely due to the low dose rate, to the fractionated irradiation, or to concurrent treatment with antibiotics or bone marrow infusion. Furthermore, neutron radiation is much more destructive to intestinal crypt cells than are similar quantities of γ-photons. Once injury to the gastrointestinal tract has reached sufficient levels to produce symptoms associated with the acute radiation syndrome, mechanisms of organ failure and interventions would be expected to be the same regardless of the circumstances of their origin. Therefore, this review reports primarily data obtained from experiences with photons delivered promptly, as may occur in an accident. However, these findings should be pertinent to any situation in which the total dose received and the dose rate are above a given threshold.

Pathophysiology of Gastrointestinal Injury

Acute Radiation Sickness or Prodromal Syndrome

Immediately after total body irradiation with doses >1.5 Gy, vomiting is frequently observed in all the mammals that can vomit, i.e., cats, dogs, monkeys, and humans, but not in those that cannot, such as rats and mice (7). The median effective dose for vomiting is ~2 Gy for total body exposure to γ-rays; it is believed to be ~2 Gy for neutron irradiation also, although some differences may exist in animals (8). In humans, radiation-induced vomiting is preceded and accompanied by nausea and anorexia (1,4); in animals, hypersalivation, chewing, and yawning are observed, and these symptoms may be considered to be the physiologic equivalents of nausea (9). In addition, gastric emptying, gastric motility, and gastric secretion are temporarily suppressed (10,11). For doses >9 Gy, diarrhea is often observed, and the prognosis is particularly poor if diarrhea is explosive and bloody. These symptoms may be explained by the gross alterations of the myoelectric activity of the small intestine that were observed in dogs exposed to 9.4-Gy abdominal γ-radiation; an initial increase of intestinal motility immediately after exposure was followed by decreased motility 1–4 days later (12).

These symptoms are potentially important from a diagnostic standpoint because they can be used within 1 or 2 h of exposure to qualitatively estimate the dose of radiation received. Similar symptoms are observed after local irradiation, although to a lesser extent. In the case of local irradiation, the threshold for vomiting and diarrhea is lowest for the abdomen, the irradiation of which causes nausea and vomiting after doses greater than about 1.5 Gy (8).

The mediators involved in these early effects of radiation are unknown. Direct or indirect radiation effects on the central nervous system probably play a pivotal role, although areas of the brain that are involved remain ill defined, as is the nature of the neurotransmitters mediating these effects (13). The vomiting center and the vagal nuclei are thought to be necessary, but the precise role of the area postrema is still controversial (14–16). The stimulation of the central nervous centers could result from the radiation-induced release of free radicals, or from other substances such as the endotoxins produced by intestinal microorganisms that have been shown to enter the bloodstream of animals (17) and humans (18) after irradiation. Alternatively, the peripheral afferent nerves could be directly stimulated by these endogenous substances. Whatever initiates the general response of the body, a release of various circulating chemicals (i.e., β-endorphin, histamine, prostaglandins, endotoxins) has been observed after total-body irradiation, but their role in producing the early effects of radiation remains to be defined. β-Endorphin could play a role because endogenous and exogenous opiates are known to cause vomiting (19), to slow gastric emptying, and to suppress gastric acid output (20). The role of histamine in the pathogenesis of the symptoms of the prodromal

syndrome remains unclear and probably involves histamine H_1-receptors; histamine H_2-receptor agonists do not cause vomiting and they stimulate gastric secretion and gastric emptying (21), whereas the opposite is observed after total-body irradiation (11). In contrast, prostaglandins could be candidates as mediators of the observed symptoms because (a) they are released after irradiation (22,23) and (b) their effects are similar to those occurring after total-body irradiation (24,25). Finally, the fact that combined vagotomy and high spinal cord section prevents radiation-induced vomiting (16) suggests that an afferent or efferent nervous mechanism, or both, is involved, although the neurotransmitter mediating this effect has not yet been defined (26). In general, there are no morphologic changes of gastrointestinal smooth muscles or intestinal mucosa during the prodromal syndrome (12), although some alterations of parietal cell ultrastructure have been described (11).

Subacute Gastrointestinal Syndrome

Radiation-induced vomiting usually ceases within 24 h of total-body irradiation, and gastric function is normal 2 days after 8-Gy γ-exposure (11). Patients and animals then experience a relatively symptom-free period that may last 2–7 days, depending on the dose received. If this dose is >5 Gy, a second phase of radiation sickness appears within 1 wk of irradiation. One observes stomatitis, abdominal bloating, gastrointestinal ileus, diarrhea, and guaiac-positive or bloody stools (4) as well as sepsis, dehydration, and shock. This syndrome is characterized by electrolyte imbalance (27,28) and, as shown by metabolic balance studies (3), bears similarities with the situation observed during the postoperative period and after surgical injury.

The cause of these symptoms is complex, and their pathogenesis is still not completely understood. After doses of radiation >2 Gy, the turnover of intestinal cells is decreased, leading to atrophy of the villi (4). In addition, radiation produces alterations of transport in the rabbit ileum as evaluated in vitro with Ussing chambers. Short circuit current, transepithelial potential, and resistance were all increased dose-dependently 1–4 days after total-body exposure to 7.5–12-Gy γ-radiation (29). These changes are similar to those observed after administration of bacterial toxins or secretagogues, and they may be responsible for decreased intestinal absorption of electrolytes, fluids, and nutrients in vivo (30,31).

An intestinal injury with immunologic and physiologic consequences is increased permeability of the epithelial barrier. This concept is consistent with findings of Fine and coworkers (32–34), who detected bacterial endotoxin of intestinal origin in the plasma of animals after a variety of severe trauma episodes. Endotoxin-containing particles in the intestine may penetrate the epithelial barrier via the intercellular route. The incidence of disrupted intercellular tight junctions followed a biphasic pattern similar to that seen for the detection of endotoxin in mouse livers after irradiation (35). This increase in intestinal permeability after irradiation could be due to the action of humoral mediators on this organ. A variety of vasoactive substances have been shown to increase intestinal permeability to endotoxin (36). For example, severe disruption of the tight junction complex was seen in rabbits infused with histamine but not in those animals given saline (37).

Although not always associated directly with mortality, endotoxin may have profound effects on radiation victims. For example, endotoxins may contribute to immunosuppression in the host, but they can also produce subsequent beneficial effects in compromised subjects (38), such as stimulation of bone marrow repair after irradiation (39). Sublethal endotoxemia may be beneficial in other types of trauma as well. For example, Spillert et al. (40) reported that endotoxin decreased burn severity when given to mice immediately after thermal injury. On the other hand, endotoxins released shortly after irradiation of animals (17) or humans (18) may also contribute to early performance decrements associated with radiation.

Endogenous enteric bacteria appear not to play a major role in pure intestinal radiation death described after doses >12 Gy as there was no sepsis or endotoxemia at the time of death in rats with acute intestinal injury (41). Furthermore, preirradiation contamination of the gastrointestinal tract with *Pseudomonas aeruginosa* did not modify survival time of animals dying from pure intestinal syndrome within 3–4 days of irradiation (42). In contrast, postirradiation infection from endogenous enteric bacteria was an important factor after exposure to the lower doses of radiation that cause later death by a combination of intestinal and hemopoietic injuries (42).

Intestinal microorganisms are a major source of infection in irradiated individuals. Changes in the numbers of facultatively anaerobic bacteria, which could become opportunistic pathogens after irradiation, have been monitored in experimental animals (35). Ilea were removed from rats at intervals after sublethal (5 Gy) or lethal (10 Gy) cobalt 60 irradiation and cultured quantitatively for microorganisms. The facultative flora were significantly reduced in numbers 24 h after sublethal irradiation but reached preirradiation levels 7–11 days later. Lethal (10 Gy)

radiation also caused a reduction in numbers of facultative flora at 24 h after irradiation but, in contrast to sublethally irradiated rats, facultative populations began to increase by 7 days postirradiation and were increased several times above normal levels by day 11. This period of excessive colonization of the ileum by facultatively anaerobic flora coincided with the beginning of the time that deaths occurred in rats. Disturbed intestinal microecology has also been seen in other animal models of irradiation injury and has been associated with sepsis and death (35). Changes in the intestinal flora, coupled with impairment of the normal barrier function of the gastrointestinal tract, allow the bowel to serve as a reservoir for pathogens that can enter the portal and systemic circulations and fuel the ongoing septic process. This process may become rapidly overwhelming in a subject further compromised by marrow failure and profound immunosuppression.

In addition, loss of colonization resistance is associated with shifts in microbial populations in compromised individuals. Van der Waaij (43) has shown that opportunistic pathogens in the digestive tract are the major source of infection in animals with decreased defensive capacity. Colonization-resistant anaerobic flora contribute to the control of these facultatively anaerobic pathogens, but when colonization resistance is lost, the opportunistic flora are able to multiply excessively on mucosal surfaces. This event is associated with invasion of normally sterile tissues by endogenous flora. Selective decontamination of the digestive tract with antibiotics that eliminate pathogens but do not disturb anaerobic flora (which maintain colonization resistance) has successfully been used to prevent infection in patients with burns (44) or granulocytopenia (45).

There is a relationship between numbers of intestinal microorganisms and their translocation to mesenteric lymph nodes (46). Increased numbers of bacteria in the lumen of irradiated subjects could cause opportunistic infections through this process. Recent data may help identify the route by which translocation occurs, suggesting that M cells overlying lymphoid follicles of the gastrointestinal tract are part of a major antigen-sampling system (47). Some bacteria can attach to and be transported through these cells, where they should be processed by macrophages and lymphocytes as an initial step in the mucosal immune response. If the normal function of this system is impaired by radiation or other trauma, an easy route of ingress to the body would be provided.

Many organisms colonizing the intestine, including those conferring colonization resistance, are localized in the mucous barrier, a major structure 450 μm thick overlying the epithelium (48). Any alteration of normal intestinal barrier function could enhance the likelihood of systemic infection as well as permit intestinal contents to damage the epithelial lining. Irradiation may cause a reduction of mucus secretion either through a decrease in the number of goblet cells in the mucosa or through lymphocyte (T cell) loss from radiation exposure (49). Bile secretion could also affect mucus integrity (50). Although the mechanism is unknown, it was recently shown that the continuity of the mucous blanket can be degraded after irradiation (51). Although other physiologic and immunologic changes are probably also involved in influencing postirradiation microbiologic events in the intestine, destruction of the mucous barrier could alter colonization resistance and permit pathogen access to the epithelium.

Alterations of Intestinal Blood Flow and Microcirculation

The role of alterations of intestinal blood flow in the pathophysiology of the acute, subacute, and chronic radiation syndromes remains unclear. Measurements of total small intestinal blood flow in rats exposed to 5-Gy total-body γ-radiation failed to demonstrate consistent changes. In contrast, intestinal blood flow decreased during the first 2 h after exposure to 10 Gy but increased significantly by 4–6 h postirradiation (52–54). In rats exposed to whole-body γ-radiation of either 9 or 10 Gy, Suskevic and Uklonskaya (55) observed marked fluctuations in blood flow in the first hours after irradiation. An initial decrease was followed by a pronounced increase at 6 h postirradiation and then by a sharp decrease from the second to the third day.

Extended observations of postirradiation blood flow to the small intestine showed a continued decrease at 6 and 12 mo after abdominal x-irradiation, with a fractionated (1.91 Gy/day) exposure of 28.71 Gy. However, both the jejunum and ileum showed a blood flow at control level when exposed to only a single dose of 5.74 Gy x-radiation (56). In contrast, blood flow to the large intestine was increased through the 6 mo of postirradiation observation, but began a decline to below control levels by 12 mo postirradiation.

Thus, variations exist according to the species, organs, source of radiation, method of exposure (fractionated or single), technique of blood flow measurement, and time of measurement after irradiation. The response appears to be triphasic after exposure to doses ~6 Gy: an initial decrease in blood flow is followed in a few hours by an increase that lasts a few days and, in turn, gives way to a long-lasting decrease in total blood flow.

The microcirculation of the intestine also appears

to be altered after irradiation. Seventy-two hours after exposure to 15-Gy mixed neutron–γ-radiation, the villous capillary network of the dog small intestine appeared histologically intact and continuous, despite mucosal cell destruction, but the intestinal capillary blood flow per gram of mucosa was increased at that time (57). Occlusive endothelial changes were found in the submucosal arterioles of rats 4 days after exposure to 14.6-Gy x-radiation (58). Similarly, clinical evidence of microvascular changes in humans with radiation bowel disease has been furnished by Carr et al. (59). These studies also indicated that alterations were observed in the mucosal vasculature in patients 1–28 mo after radiotherapy. In addition, Suskevic and Uklonskaya (55) observed that permeability increased fourfold in rats 3 days after exposure to whole-body γ-radiation of 9–10 Gy.

In cats exposed to doses of up to 15 Gy, the microvasculature of the intestine was found to be normal 4 days to 4 mo postirradiation (60). However, after exposure to 15–30 Gy, decreased vascularity was observed in all layers of the bowel, including variations in luminal width and obstruction of vessels, which occurred more frequently at the higher doses (60). These vascular changes may be responsible for a decreased capillary filtration coefficient, which has been observed after irradiation. In addition, later experiments provided evidence of ultrastructural changes that correlated with these changes in capillary filtration coefficient, suggesting that the early decrease in this coefficient seen in the groups exposed to 20 and 25 Gy may result from pericapillary fibrosis.

Prospects for Management

Prodromal Syndrome

The prevention and treatment of radiation-induced vomiting can be achieved with neuroleptics (chlorpromazine, promethazine) or even general anesthesia (61). However, this type of approach is not desirable because of the side effects of these medications, which further depress gastric emptying and appetite and may increase the risk of pulmonary infection.

A more promising approach has been the use of antidopaminergic agents. The oldest dopamine antagonist is metoclopramide which, in addition to its antiemetic properties, has a potent gastrokinetic effect and prevents radiation-induced vomiting and gastroplegia in monkeys (62). This gastrokinetic action appears to be independent of its antidopaminergic properties and may be related to a metoclopramide-induced release of acetylcholine and other neuropeptides within the myenteric plexus (63). However, therapeutic doses of metoclopramide do not seem to be effective in humans if given after vomiting has started (64). In addition, this medication may cause extrapyramidal side effects, because it crosses the blood-brain barrier and inhibits striatal dopamine receptors (65). In contrast, the peripheral dopamine antagonist domperidone does not cause central side effects because it inhibits only the dopamine receptors located outside the blood-brain barrier (66) and it prevents radiation-induced vomiting in the dog (10). However, domperidone does not appear to be effective against either radiation-induced gastroplegia or radiation-induced vomiting in the monkey (10,11). In contrast, clinical trials seem to indicate that domperidone may be effective in humans (67), although double-blind placebo-controlled studies will be necessary to confirm this finding.

A number of newer antiemetic and gastrokinetic agents are currently being tested in both animals and patients. Recently, one of these medications (Zacopride, A. H. Robins Co., Richmond, Va.) was found to be effective in the prevention and treatment of the prodromal syndrome (vomiting, retching, and gastric emptying suppression) in monkeys while not causing undesirable side effects (68).

Subacute Radiation Syndrome

The treatment of the subacute gastrointestinal syndrome is based on supportive therapy to prevent infection and dehydration, although ultimate survival depends on bone marrow and intestinal stem cell restoration or repopulation. This therapy includes plasma volume expansion, platelets, and antibiotics, which enhance survival after intestinal injury caused by radiation. With these therapeutic measures, survival may be possible up to 15 Gy, but total-body irradiation above 20 Gy is not manageable. Finally, the prognosis becomes much more serious if irradiation injury is combined with thermal or mechanical injury, as may occur in an accident such as the Chernobyl disaster.

Current research is attempting to prevent the damage to the intestine by using a variety of radioprotectants. These compounds appear to reduce initial damage to stem cells in the crypts and thereby decrease the effect of a given dose of radiation. Under experimental conditions a dose reduction factor can then be calculated to quantitatively evaluate the efficacy of radioprotectants. For example, the thiol derivative group (ethiofos or WR-2721) improves survival of the stem cells of the intestinal crypts in addition to those of the bone marrow and has a dose reduction factor of 1.25 1.60 (31,69). Furthermore, ethiofos enemas in rats demonstrated a

dose reduction factor of 1.8 compared with controls (70). As the compound was not absorbed into the circulation, it appears that ethiofos can exert its radioprotective action by a direct, nonsystemic effect on gastrointestinal mucosa. Recent evidence has also been presented suggesting that the use of prostaglandins alone and especially in combination with WR-2721 could prevent damage to the epithelial cells of intestinal villi, being therefore truly radioprotective and cytoprotective (69).

Stem cell survival in the intestine is a probable event, even if radioprotectants are not used. For this reason, the induction or administration of cell growth regulators after radiation offers future possibilities for enhancement of intestinal recovery. This approach is already being applied to the stem cell compartment of the bone marrow of irradiated subjects (71).

Other methods to promote intestinal recovery may be closer at hand. Postirradiation enteropathy is exacerbated by bile and pancreatic proteases (72,73). Effects of these substances may be enhanced when the mucous barrier is lost after injury (51,74). These problems can be alleviated and cellular recovery enhanced in experimental animals fed elemental diets containing amino acids before irradiation (74–76). Finally, therapeutic effectiveness of elemental diets has also been shown in patients undergoing radiation therapy (77), and numerous other compounds such as micronutrients (e.g., selenium, vitamins A and E) are also currently under study as potential radioprotectants.

Summary

Three types of injury occur in the gastrointestinal tract after radiation. Emesis and gastric suppression are caused by mechanisms still unknown, and have effects that complicate radiotherapy and the treatment of people receiving exposures in accident or weapon detonation scenarios. Sufficient damage to the epithelial barrier and the intestinal microcirculation impairs gastrointestinal function, which can have lethal consequences. The mucosal immune system and the ecology of the colonization resistant flora are also disrupted after radiation exposure. Thus, mortality and morbidity are increased by infectious complications, as well as physiologic failure.

Progress is being made to control the physiologic and immunologic consequences of radiation injury to the gastrointestinal tract. New-generation antiemetics may soon control some debilitating effects of radiation. Furthermore, supportive therapy with fluids and platelets, as well as controlled diets, can now minimize some radiation injury. Radioprotectants, possibly in combination with growth factors that enhance stem cell recovery, may soon be available to prevent or to rapidly repair gastrointestinal damage. Selective decontamination with poorly absorbed antibiotics can now offset some consequences of immune suppression in the intestine and future studies may reveal means to nonspecifically enhance mucosal immunity as systemic immunity can now be stimulated.

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